REMARKS

Claims 11-14, 16, 20-27, 32-24, 36, 37, 44 and 50-66 are pending and under examination.

With this amendment, claims 16, 25, 27, 34, 44, and 55 have been amended; claims 14 and 37 have been canceled without prejudice; and new claims 67-99 have been added. Support for the new claims can be found, for example, in previously presented claims before amendment and in the specification as filed on page 25, lines 17-22. Accordingly, the amendments and new claims do not raise an issue of new matter and entry thereof is respectfully requested.

Rejection Under 35 U.S.C. § 102(b)

The rejection of claims 11, 13, 14, 16, 21, 22, 24-27, 32, 34, 36, 37, 44 and 50-61 under 35 U.S.C. § 102(b) as allegedly anticipated by Turner et al., Breast Cancer Res. Treatment 46:69 (1997), is respectfully traversed.

Applicant respectfully asserts that the claims, as amended, are directed to methods that include determining the level of BAG-1 expression in stage I of breast cancer. According to MPEP § 2131, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. Turner et al. does not teach or suggest BAG-1 expression in stage I of breast cancer. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) of claims 11, 13, 14, 16, 21, 22, 24-27, 32, 34, 36, 37, 44 and 50-61.

With regard to new claims 67-99, applicant respectfully asserts that the claims are directed to methods that include determining the level of BAG-1 expression in stage II of breast cancer with no lymph node involvement. The specification teaches, for example, the definition of stage II breast cancer on page 25, lines 17-22, and refers on the same page relating to breast cancer staging system to the reference Markman 1997, Basic Cancer Medicine; pp 35-36 (pp. 35-37 of Markman attached as Exhibit 1). Turner et al. does not teach or suggest BAG-1 expression in stage II of breast cancer with no lymph node involvement. Absent such a teaching, Applicant respectfully avers that Turner et al. cannot anticipate new claims 67-99.

Rejection Under 35 U.S.C. § 103

The rejection of claims 11-14, 16, 21, 22, 24-27, 32-34, 36, 37, 44 and 50-61 under 35 U.S.C. § 103 as allegedly obvious over Turner et al., *supra*, in view of Sano et al., U.S. Patent No. 5,665,539, is respectfully traversed. Applicant respectfully maintains, for the reasons of record and further as set forth below, that the claims are unobvious over the cited references whether viewed individually or in combination.

As discussed above, Turner et al. neither teaches nor suggests the claimed methods relating to stage I of breast cancer. Sano et al. does not cure this defect either, as it contains no teaching or suggestions that would complement the teaching of Turner et al. with regard to stage I of breast cancer. Therefore, Applicant respectfully maintains that the claimed methods are unobvious over Turner et al., alone or in combination with Sano et al. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

The rejection of claims 11, 13-14, 16, 20-22, 24-27, 32, 34, 36, 37, 44 and 50-66 under 35 U.S.C. § 103 as allegedly obvious over Turner et al., *supra*, in view of Sauter et al., Br. J. Cancer 76:494-501 (1997), is respectfully traversed. Applicant respectfully maintains, for the reasons of record and further as set forth below, that Turner et al., alone or in combination with Sauter et al., does not teach or suggest the claimed methods.

As discussed above, Applicant respectfully maintains that Turner et al. does not teach or suggest the claimed methods relating to stage I of breast cancer. Furthermore, Applicant respectfully maintains that Sauter et al. does not cure the deficiencies of Turner et al. in teaching stage I of breast cancer. Therefore, Applicant respectfully maintains that the claimed methods are unobvious over Turner et al., alone or in combination with Sauter et al. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

The rejection of claims 11, 13, 14, 16, 21-27, 32, 34, 36-37, 44 and 50-61 under 35 U.S.C. § 103 as allegedly obvious over Turner et al., *supra*, in view of Takayama et al., Cancer Res. 58:3116-3131 (1998), is respectfully traversed. Applicant respectfully maintains, for the reasons of record and further as set forth below, that Turner et al., alone or in combination with Takayama et al., does not teach or suggest the claimed methods.

As discussed above, Applicant respectfully maintains that Turner et al. does not teach or suggest the claimed methods relating to stage I of breast cancer. Furthermore, Applicant respectfully maintains that Takayama et al. does not cure the deficiencies of Turner et al. in teaching stage I of breast cancer. Therefore, Applicant respectfully maintains that the claimed methods are unobvious over Turner et al., alone or in combination with Takayama et al. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

The new rejection of claims 11, 13-14, 16, 20-22, 24-27, 32, 34, 36-37, 44 and 50-66 under 35 U.S.C. § 103 as allegedly obvious over Turner et al., *supra*, in view of Love, U.S. Patent No. 6,221,622, is respectfully traversed. Applicant respectfully submits that Turner et al., alone or in combination with Love does not teach or suggest the claimed methods.

As discussed above, Applicant respectfully maintains that Turner et al. does not teach or suggest the claimed methods relating to stage I of breast cancer. Furthermore, Applicant respectfully avers that Love does not cure the deficiencies of Turner et al. in teaching BAG-1 expression in stage I of breast cancer. All Love does is to teach a method of obtaining fluids, marker substances and cellular material from single milk ducts in the breast of a patient for cancer diagnosis. Therefore, Applicant respectfully maintains that the claimed methods are unobvious over Turner et al., alone or in combination with Love. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

With respect to new claims 67-99, as discussed previously, Applicant respectfully avers that Turner et al. fails to teach or suggest BAG-1 expression in stage II of breast cancer with no lymph node involvement. None of the other references, Sano et al., Sauter et al., Takayama et al., or Love cures this defect. Therefore, Turner et al. cannot be combined with either of Sano et al., Sauter et al., Takayama et al., or Love to arrive at the methods of new claims 67-99. As such, Applicant respectfully submits that new claims 67-99 are also unobvious over Turner et al. alone or when combined with other cited references.

In light of the amendments and remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully requests a notice to this effect. The Examiner is invited to call the undersigned agent if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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**EXHIBIT 1**

# BREAST CANCER

## OVERVIEW

- Approximately 200,000 new cases in the U.S. each year; recent increase in incidence largely due to smaller primary tumors being discovered through *screening mammography.*
- Most common cancer in women; second most common cause of death from cancer (after lung cancer) in women.
- Two thirds of patients with breast cancer have no evidence of lymph node involvement at diagnosis.

## UNIQUE FEATURES

- Important *prognostic factors* in breast cancer include size of primary breast lesion, presence of axillary adenopathy, number of axillary nodes involved with cancer, tumor differentiation (cytoplasmic and nuclear grade), presence or absence of hormone (estrogen and progesterone) receptors.
- For women with small breast cancers (≤1 cm maximum diameter) without axillary involvement, the long-term survival is excellent (9% recurrence at 10 years).
- The extent of axillary node involvement is the *strongest* predictor of risk for recurrence and of survival. For example, independent of tumor size, 70% of women with *negative* axillary nodes at the time of surgery survive 10 years. In contrast, for women treated with surgery only (no adjuvant chemotherapy), 10-year survival with 1–3 involved axillary nodes is 40%, as compared with only 15% for women with >4 involved nodes.
- While morphologic tumor type does not appear to have an important effect on prognosis, independent of those factors noted above, the less common breast tumor types (e.g., tubular, mucinous, papillary carcinoma) appear to have an overall superior prognosis.

## DIAGNOSTIC EVALUATION

### Screening

- Brief history and physical examination of the breast, followed by mammography.

### Presence of Breast Lump

- History and complete physical examination (focusing on breast, axilla) followed by mammography (for evidence of tumor multicentricity or bilateral breast involvement). In addition, routine complete blood count, liver function tests, and chest film are appropriate. There is *no* indication that routine liver or bone scans or CT of the abdomen or chest provides additional information in asymptomatic patients with normal liver function tests and a normal chest film.

### Evidence of Potential Metastatic Spread

- Patients with any indication of metastatic tumor involvement at presentation should have appropriate diagnostic tests. For example, those with bone pain or elevated alkaline phosphatase should have a bone scan.

## STAGING (TNM System)

### Primary Tumor (T)

| | | |
|---|---|---|
| TX | Primary tumor cannot be assessed | |
| T0 | No evidence of primary tumor | |
| Tis | Carcinoma *in situ:* intraductal carcinoma, lobular carcinoma *in situ*, or Paget's disease of the nipple with no tumor (Paget's disease with tumor is classified according to tumor size) | |
| T1 | Tumor ≤2 cm in greatest dimension | |
| | T1a | ≤0.5 cm in greatest dimension |
| | T1b | >0.5 cm, but ≤1 cm in greatest dimension |
| | T1c | >1 cm, but ≤2 cm in greatest dimension |
| T2 | Tumor >2 cm but ≤5 cm in greatest dimension | |
| T3 | Tumor >5 cm in greatest dimension | |
| T4 | Tumor of any size with direct extension to the chest wall or skin | |
| | T4a | Extension to the chest wall |
| | T4b | Edema (including *peau d'orange*) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast |
| | T4c | Both (T4a and T4b) |
| | T4d | Inflammatory carcinoma |

### Regional Lymph Nodes (N)

| | |
|---|---|
| NX | Regional lymph nodes cannot be assessed (e.g., previously removed) |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis to movable ipsilateral axillary lymph node(s) |
| N2 | Metastasis to ipsilateral axillary lymph node(s) fixed to one another or to other structures |
| N3 | Metastasis to ipsilateral internal mammary lymph node(s) |

### Distant Metastasis (M)

| | |
|---|---|
| MX | Presence of distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis (also includes metastasis to ipsilateral supraclavicular lymph nodes) |

### Stage Grouping

| | | | |
|---|---|---|---|
| Stage 0 | Tis | N0 | M0 |
| Stage I | T1 | N0 | M0 |
| Stage IIA | T0 | N1 | M0 |
| | T1 | N1 | M0 |
| | T2 | N0 | M0 |
| Stage IIB | T2 | N1 | M0 |
| | T3 | N0 | M0 |
| Stage IIIA | T0 | N2 | M0 |
| | T1 | N2 | M0 |
| | T2 | N2 | M0 |
| | T3 | N1,N2 | M0 |
| Stage IIIB | T4 | Any N | M0 |
| | Any T | N3 | M0 |
| Stage IV | Any T | Any N | M1 |

## TREATMENT

### Primary Breast Cancer

Goals of primary treatment of breast cancer are removal of macroscopic tumor, treatment of microscopic local and regional disease, and to minimize morbidity of treatment (both functional and cosmetic). These goals can be successfully accomplished though several strategies, including:

- Modified radical mastectomy (breast and axillary contents removed with preservation of pectoralis muscles). This procedure may be followed by breast reconstruction.
- Partial mastectomy, axillary dissection, and breast irradiation. (Breast-preserving procedure removes all known macroscopic tumor; radiation is employed to treat residual microscopic disease.) Radiation can be by external beam only or may involve a "boost" to the area of initial tumor involvement with an interstitial implant.
- The decision to remove the breast, either partially or completely, depends on several factors, including the size of the tumor relative to the size of the breast (i.e., will the amount of residual normal breast tissue result in a favorable cosmetic result as compared with reconstruction of a new breast?), multifocal breast cancer (favoring total breast removal), and patient choice (e.g., complete removal of tissue without radiation versus partial removal and the requirement for several weeks of radiation treatment).

### Adjuvant Therapy (Hormonal or Chemotherapy)

- Data from >125 randomized trials involving >75,000 women with breast cancer have documented the role of both *adjuvant* chemotherapy and hormone therapy in prolonging both disease-free survival and overall survival in early-stage breast cancer. In general, chemotherapy is employed as adjuvant treatment in premenopausal women, whereas either chemotherapy or hormone therapy (or both) is employed in postmenopausal patients with breast cancer.
- In women with *node-negative breast cancer,* treatment with tamoxifen (an "antiestrogen" hormone) resulted in a 26% ±4% (SD) reduction in disease recurrence and a 17% ±5% decrease in mortality. Combination chemotherapy in this setting resulted in a 26% ±7% decrease in tumor recurrence and an 18% ±8% improvement in survival.
- The benefits of adjuvant therapy for *node-positive breast cancer* are greatly influenced by the number of positive nodes found at surgery. The overall percent reduction in recurrence is approximately 24–30% and the decrease in mortality 15–20%.

### Treatment of Metastatic Disease

- A number of cytotoxic drugs have demonstrated significant activity against breast cancer (e.g., doxorubicin, paclitaxel, docetaxel, alkylating agents). In a woman with good performance status and relatively low tumor burden, the anticipated objective response rate to several combination regimens (e.g., cyclophosphamide, methotrexate, 5-fluorouracil [CMF]; cyclophosphamide, doxorubicin, 5-fluorouracil [CAF]) is approximately 50–70%. In patients with poor performance status at the initiation of treatment, the response rate drops to 10–25%. The median duration of response in metastatic disease is 9–12 months.
- Hormone therapy (e.g., tamoxifen, megestrol acetate) is effective in women with estrogen and progesterone receptor–positive tumors. In the absence of receptor positivity, the objective response rate to a variety of hormonal regimens is <10%; however, if both receptors are present in a tumor, the response rate increases to 60–80%. As with chemotherapy, the duration of response is generally 9–12 months.
- Unfortunately, <5% of patients with metastatic breast cancer remain in remission for >10 years. Median survival for patients who fail to respond to initial chemotherapy is <6 months.

## NEW DIRECTIONS

- Additional prognostic factors have been suggested to be significant in breast cancer. These include *HER-2 neu* oncogene expression, epidermal growth factor expression, altered P53 suppressor gene, evidence of extensive angiogenesis in the tumor, and cathepsin D expression. It remains unknown at present if these factors provide clinically relevant information beyond that already obtained with knowledge of tumor grade, axillary node involvement, and hormone receptor status. These, and other new factors, remain in the clinical development stage.
- High-dose chemotherapy with bone marrow or peripheral progenitor cell support (to rescue the marrow from the myeloablative effects of the cytotoxic agents) is a promising investigative approach to management of both metastatic breast cancer and women at high risk for developing recurrent disease. Preliminary data from nonrandomized trials of this strategy in both the metastatic and adjuvant settings suggest that survival may be prolonged, as compared with that of historical control groups.

### Suggested Additional Reading


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